# CAN MIDAZOLAM DIMINISH SUFENTANIL ANALGESIA IN PATIENTS WITH MAJOR TRAUMA? A RETROSPECTIVE STUDY WITH 43 PATIENTS

Thomas J. Luger[1,2], Harlan F. Hill[3†] and Andreas Schlager[2]

[1]*Department of Anesthesiology, School of Medicine*
*University of Washington, Seattle, WA, USA*
[2]*Clinic of Anesthesia and General Intensive Care Medicine*
*University of Innsbruck, Austria*
[3]*Division of Clinical Research*
*Fred Hutchinson Cancer Research Center*
*Seattle, WA, USA*

**ABSTRACT**

Benzodiazepine agonists in combination with opioid analgesics are commonly used for combined analgesia and sedation in intensive care patients as well as for anesthesia. In animals, studies indicate either agonistic or antagonistic interactions of benzodiazepine agonists and opioids. This retrospective study of 43 patients evaluated the possible clinical relevance of benzodiazepine-opioid interactions related to pain management. We observed an increase of $>50\%$ of the maximal sufentanil infusion rate in significantly more patients in group 2 (13 patients vs 6 patients; $\chi^2$: $p = 0.04$) and a decrease of the sufentanil infusion rate in eight group 1 patients, but only in one patient in group 2 ($\chi^2$: $p = 0.03$). We believe that an interaction between midazolam and sufentanil on nociceptive transmission and/or a rapid development of tolerance to sufentanil may be responsible for the observed difference. Contrary to the common clinical impression that midazolam potentiates opioid analgesia, these

Presented in part at the annual meeting of the Society of Clinical Pharmacology and Therapeutics in San Antonio, Texas, U.S.A., 1991.

Address for correspondence:
Thomas J. Luger, M.D.
Clinic of Anesthesia and General Intensive Care Medicine
University of Innsbruck, Anichstr. 35, A-6020 Innsbruck, Austria

†deceased

results indicate that systemic co-administration of midazolam over a period of more than three days can diminish sufentanil efficacy.

**KEY WORDS**

sufentanil, benzodiazepines, interaction, intensive care unit, tolerance

## INTRODUCTION

The clinical use of benzodiazepine agonists in combination with opioid analgesics for postoperative pain control has gained wide acceptance among anesthesiologists. Benzodiazepine agonists induce sedation, reduce anxiety and provide useful amnesia for unpleasant and painful procedures /1/. The antinociceptive effect of morphine given systemically to rats is diminished after intracerebroventricular administration of diazepam or midazolam using the tail flick test as the endpoint /2/. Conversely the administration of morphine and a small dose of midazolam intrathecally produced greater antinociception than the administration of morphine alone /3, 4/. After systemic administration of both drugs in laboratory animals, either an increase /5/ or a decrease /6/ in opioid analgesia has been reported. However, Abbott and Franklin observed that diazepam given systemically antagonizes morphine analgesia in the formalin test but has no effect in the tail flick test /7/. The aim of this retrospective study was to evaluate the possible clinical relevance of benzodiazepine-opioid interactions related to pain management.

## METHODS

We analyzed results from 43 intensive care patients with major trauma, who required mechanical ventilation. Twenty two (group 1: age = 35.4 ± 14.3 years; body weight = 77.9 ± 16.1 kg) received infusions of sufentanil alone. In the other 21 patients (group 2: age = 31.0 ± 12.3 years; body weight = 71.9 ± 9.6 kg), this regimen was supplemented by a midazolam infusion (0.07 mg/kg/h).

The initial dose of sufentanil was 1 $\mu$g/kg/h in both groups; in group 2 midazolam was administered at different timepoints (39.1 ± 18.0 hours) after initiation of the sufentanil infusion. During

the period of ventilation, patients received parenteral nutrition and various other drugs, including muscle relaxants, heparin, cimetidine, hydrocortisone, dopamine and dobutamine. All changes of the sufentanil infusion rate were made when the patient showed more than two of the following signs: tachycardia >20% from the baseline, hypertonia >20% from baseline, vegetative symptoms, movements of the body, respiratory problems or the patient fought against the respirator. When treating with increased sufentanil infusion rate, if the desired effect was not reached, the sufentanil infusion was supplemented with a midazolam infusion.

Comparisons between the groups were carried out with the Wilcoxon signed rank test. Percent change of sufentanil infusion rate data were analyzed by Yates corrected $\chi^2$ for 2x2 contingency tables. For within-group analyses linear correlation coefficients and regression equations were used. Significance was accepted at $p \leq 0.05$. All data of group 2 are for the time period beginning with the first midazolam administration. During the time before midazolam administration, there were no significant differences with respect to initial sufentanil infusion rate (group 1: $1.17 \pm 0.4$ μg/kg/h; group 2: $0.94 \pm 0.3$ μg/kg/h) and maximum absolute change of sufentanil infusion rate (group 1: within the first three days $1.56 \pm 0.9$ μg/kg/h; group 2: $1.57 \pm 0.7$ μg/kg/h), or liver function and renal function between group 1 and group 2 patients (results not shown).

## RESULTS

As shown in Figure 1, more sufentanil-treated patients receiving midazolam (group 2) required an increase of opioid infusion rate, compared to patients receiving sufentanil alone. We observed an increase of >50% of the maximal sufentanil infusion rate in significantly more patients in group 2 (13 patients vs 6 patients; $\chi^2$: $p = 0.04$). It was possible to decrease the sufentanil infusion rate in eight group 1 patients, but only in one patient in group 2 ($\chi^2$: $p = 0.03$).

We observed a significant correlation between percent maximum change of sufentanil infusion rate and the duration of midazolam infusion (Table 1). We found no significant correlation between percent maximum change of sufentanil infusion rate and the duration of sufentanil infusion, injury severity score, liver function or renal

**TABLE 1**

Relationships between sufentanil requirement, midazolam administration and patient status. Comparisons between the groups were analyzed with Wilcoxon signed rank test: * $p \leq 0.05$; ** $p \leq 0.01$. Within group results were analyzed by linear regression of percent maximum change of sufentanil infusion rate versus duration of infusion, injury severity liver function or renal function parameters. Gamma GT = gamma glutamyl transpeptidase, SGOT = serum glutamine-oxaloacetic transaminase; SGPT = serum glutamic-pyruvic transaminase; Urine volume ≥ 100 ml/h in group 1 and group 2.

| | Between Groups (mean [SEM]) | | | | | Within group (Correlation coefficient r) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Group 1 | | Group 2 | | p | Gr. 1 | p | Gr. 2 | p | |
| Maximum absolute change of sufentanil infusion (µg/kg/h) | 1.78 | [0.29] | 2.76 | [0.33] | 0.046 * | • | • | • | • | |
| Duration of sufentanil infusion (hours) | 91.7 | [19.6] | 193.6 | [20.4] | 0.004 ** | -0.25 | 0.267 | 0.4 | 0.073 | |
| Duration of midazolam infusion (hours) | • | | 106.1 | [15.9] | • | • | • | 0.48 | 0.028 | * |

cont.

**TABLE 1 continued**

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Severity of injury: | | | | | | | | | | |
| Injury severity score | | 29.6 | [2.1] | 29.8 | [2.2] | 0.981 | -0.09 | 0.706 | -0.08 | 0.740 |
| Hospital trauma index | | 12.3 | [0.9] | 12.8 | [1.0] | 0.650 | 0.08 | 0.720 | -0.19 | 0.416 |
| Number of regions injured | | 2.5 | [0.2] | 3.1 | [0.3] | 0.172 | -0.07 | 0.743 | 0.06 | 0.783 |
| Liver- and renal function: | | | | | | | | | | |
| Bilirubin | Baseline | 26.1 | [3.6] | 29.7 | [4.4] | 0.687 | | | | |
| (μmol/l) | Change | 35.0 | [5.3] | 96.9 | [22.4] | 0.018 * | -0.25 | 0.264 | 0.37 | 0.119 |
| Gamma GT | Baseline | 17.2 | [3.6] | 27.7 | [7.6] | 0.408 | | | | |
| (U/l) | Change | 48.7 | [14.6] | 92.2 | [17.9] | 0.015 * | -0.39 | 0.084 | 0.3 | 0.226 |
| SGOT | Baseline | 46.6 | [7.7] | 49.8 | [12.6] | 0.614 | | | | |
| (U/l) | Change | 32.8 | [4.9] | 49.3 | [10.8] | 0.409 | -0.28 | 0.214 | -0.13 | 0.592 |
| SGPT | Baseline | 46.8 | [8.7] | 33.7 | [8.0] | 0.150 | | | | |
| (U/l) | Change | 38.8 | [4.9] | 63.2 | [14.2] | 0.279 | -0.09 | 0.692 | 0.004 | 0.988 |
| Creatinine | Baseline | 79.0 | [3.2] | 74.6 | [4.4] | 0.227 | | | | |
| (μmol/l) | Change | 79.2 | [3.7] | 78.6 | [6.4] | 0.538 | -0.35 | 0.113 | -0.29 | 0.251 |
| Creatinine | Baseline | 64.2 | [8.1] | 58.5 | [5.9] | 0.498 | | | | |
| Quotient | Change | 66.9 | [5.0] | 58.9 | [6.2] | 0.205 | -0.13 | 0.589 | -0.1 | 0.665 |

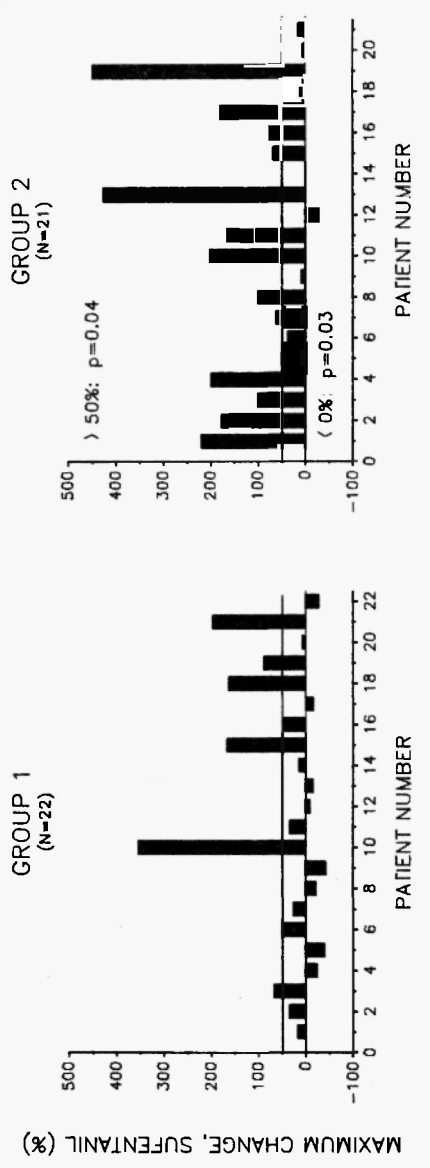


**Fig. 1:** Percent maximum change of sufentanil infusion rate in patients in group 1 (sufentanil infusion alone) and group 2 (sufentanil infusion and midazolam infusion). The mean sufentanil infusion rates (group 1 vs group 2) were not significantly different prior to the times of midazolam infusion in group 2 patients. Significantly more patients in group 2 received > 50% change ($p = 0.04$) and fewer patients received decreases (< 0%) of the sufentanil infusion rate ($p = 0.03$) compared to group 1 patients. Yates corrected $\chi^2$.

function within either group of patients, although there were significant differences between the groups for several of these parameters.

## DISCUSSION

Since variations in injury severity, liver function and renal function, or duration of opioid infusion do not appear to be responsible for our findings, possible explanations for the higher sufentanil infusion rates required in group 2 patients might be the following:

1. interaction between benzodiazepine and opioid;
2. opioid tolerance and/or benzodiazepine tolerance;
3. interaction of midazolam or sufentanil with other drugs administered, e.g. antibiotics;
4. attitudes of the staff;
5. inappropriate selection of drugs by attending staff;
6. neurological status (> 90% head injury in either group 1 or group 2);
7. metabolic status (parenteral nutrition).

We believe that an interaction between midazolam and sufentanil on nociceptive transmission (point 1 above) may be responsible for the observed difference. As noted above, various results in animal studies indicate a pharmacological interaction between opioids and benzodiazepines that can either increase or decrease opioid analgesia /2-7/. Previous clinical observations /8/ and our own findings indicate that benzodiazepine-opioid interactions following systemic administration of the drugs can have important clinical consequences, namely diminished pain control. Contrary to the common clinical impression that midazolam potentiates opioid analgesia, we found evidence to indicate that systemic co-administration of midazolam over a period of more than three days can diminish sufentanil efficacy.

In intensive care situations a benzodiazepine-opioid interaction may cause either a rapid development of tolerance to sufentanil (point 2 above) or an apparent tolerance because of the high doses of opioids used. This can also mean that, after stopping the benzodiazepine infusion, excessive systemic opioid concentrations remain. This may lead to a longer weaning phase due to prolonged

respiratory depression, to more severe withdrawal reactions, and to a longer recovery period.

On the other hand the combination of benzodiazepine agonists and opioids may be beneficial especially in the weaning phase, because benzodiazepines can mask several side effects of opioids, e.g. nausea, vomiting, feeling of sickness /9/, although midazolam does not appear to have antiemetic properties by itself /1/. It is quite possible that benzodiazepines may be used to best clinical advantage by non-systemic routes of administration, e.g. epidural injection. In reliable animal studies intrathecal benzodiazepines – in contrast to systemic benzodiazepines – are able to produce antinociception, presumably by activating benzodiazepine receptors in the spinal cord /10, 11/. Consideration of these reports leads us to suggest that midazolam may be usefully employed epidurally to increase systemic opioid analgesia in clinical pain management.

## REFERENCES


1. Reves JG, Fragen RJ, Vinik HR, Greenblatt DJ. Midazolam: Pharmacology and uses. Anesthesiology 1985; 62: 310-324.
2. Mantegazza P, Parenti M, Tammiso R, Vita P, Zambotti F, Zonta N. Modification of the antinociceptive effect of morphine by centrally administered diazepam and midazolam. Br. J Pharmacol 1982; 75: 569-572.
3. Yanez A, Sabbe MB, Stevens CW, Yaksh TL. Interaction of midazolam and morphine in the spinal cord of the rat. Neuropharmacology 1990; 29: 359-364.
4. Moreau J-L, Pieri L. Effects of an intrathecally administered benzodiazepine receptor agonist, antagonist and inverse agonist on morphine-induced inhibition of a spinal nociceptive reflex. Br J Pharmacol 1988; 93: 964-968.
5. Morichi R, Pepeu G. A study of the influence of hydroxyzine and diazepam on morphine antinociception in the rat. Pain 1979; 7: 173-180.
6. Rosland JH, Hole K. 1,4-Benzodiazepines antagonize opiate-induced antinociception in mice. Anesth Analg 1990; 71: 242-248.
7. Abbott FV, Franklin KBJ. Noncompetitive antagonism of morphine analgesia by diazepam in the formalin test. Pharmacol Biochem Behav 1986; 24: 319-321.
8. McDonald CF, Thompson SA, Scott NC, Scott W, Grant IWB, Crompton GK. Benzodiazepine-opiate antagonism – a problem in intensive care therapy. Intensive Care Med 1986; 12: 39-42.
9. Singh PN, Sharma P, Gupta PK, Pandey K. Clinical evaluation of diazepam for relief of postoperative pain. Br J Anaesth 1981; 53: 831-836.
10. Goodschild CS, Serrao JM. Intrathecal midazolam in the rat: Evidence for spinally-mediated analgesia. Br J Anaesth 1987; 59: 1563-1570.
11. Niv D, Davidovich S, Geller E, Urca G. Analgesic and hyperalgesic effects of midazolam: Dependence on route of administration. Anesth Analg 1988; 67: 1169-1173.